

ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

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Apoptosis and Hepatic Necroinflammation

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G&H In the process of apoptosis as it relates to liver injury, which liver cells are primarily affected?

GG The way that we most commonly think of hepatic apoptosis is in terms of damage to the organ. In most forms of liver injury that are clinically recognized, apoptosis occurs primarily in the hepatocytes.

There is also a potential beneficial effect of apoptosis, which occurs relative to stellate cells, the primary cells that produce collagen in the liver. If apoptosis can be promoted in this cell type, scarring of the liver can be stopped and resolution of fibrosis possibly achieved.

G&H Can you explain the mechanism by which hepatocytic apoptosis leads to fibrosis?

GG As a cell undergoes apoptosis, it is fragmented into several membrane-delineated pieces termed apoptotic bodies, which can be phagocytosed (engulfed) by neighboring cells. This process can activate the cell, which is engulfing the apoptotic body. For example, activated stellate cells have a greater propensity to produce collagen and further encourage fibrogenesis in the liver following their engulfment of these apoptotic bodies. Kupffer cells, which are the macrophages of the liver and actively engulf apoptotic bodies, also become activated and secrete cytokines and death ligands that further potentiate the apoptotic process. It is also likely that apoptotic cells will release lipids and other mediators that may activate danger signals in the surrounding cell types and promote inflammation.

G&H How does apoptosis contribute to the development of hepatic malignancy?

GG Cancer in the liver is promoted by an accelerated process of cell turnover. In healthy people, hepatocytes turn over very slowly. In disease states that promote apoptosis, the liver generates new cells at a heightened rate. It is within this proliferative process that gene alterations occur, facilitating mutations and the development and progression of cancer.

Conversely, cancer cells are subjected to considerable pressure from the immune system, which deletes transformed cells by apoptosis. Ultimately, to become a clinically relevant and established cancer, transformed cells shut off the mechanisms of apoptosis. Inhibition of apoptosis is a cardinal feature of established liver cell cancers.

G&H How do the different death receptors that facilitate hepatic apoptosis relate to the hepatic cells?

GG Hepatocytes express all three major types of death receptors: receptors for the Fas ligand, receptors for tumor necrosis factor- α , and receptors for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL). All of the ligands related to these receptors are expressed by inflammatory cells, including lymphocytes, macrophages, and other types of cells in the immune system. When inflammation occurs in the liver, these cells are attracted to the liver, where they simply activate the death receptors on the surface of the hepatocytes, resulting in cell death.

G&H How can cell-stress-related survival pathways be used to mitigate apoptosis?

GG It is known that too much stress will cause a fatal stress response and cell death. However, theoretically, a small amount of stress can strengthen cells. Data have accumulated suggesting that the initial response to cell stress is for the cell to pause, acknowledge an attack, and

defend itself, repairing damage later. This response results in the temporary avoidance of cell death. If investigators could find the fundamental mechanism for this response, we could protect the liver. Thus there is considerable research interest in agents that can provide liver-survival signals. This research is still preliminary, and it currently appears much simpler to inhibit aggressive pathways than to promote survival pathways.

G&H How can a fuller understanding of apoptosis potentially be utilized in the treatment of viral hepatitis?

GG In patients with chronic viral hepatitis, it may be possible to shut off apoptosis and prevent liver injury and scarring. There are data showing that one of the final common pathways of apoptosis is activation of intercellular proteases that digest the cell. These are termed caspases. Several pharmaceutical companies have developed caspase inhibitors, and the first caspase examined in short-term clinical trials looked very promising. It prevented liver injury in patients with hepatitis C, the patients' hepatic enzyme levels improved, and patients felt better overall. For reasons that are not currently clear, research of this agent was not further pursued by the manufacturer. However, proof of concept was established, and there are other companies with other caspase inhibitors in development and researchers who are contemplating treatment of liver disease with these agents.

G&H How can understanding of the apoptosis mechanism be applied to the treatment of hepatic cancers?

GG In patients with cancer, we need to promote apoptosis in the cancer cells. For this scenario, we have a

much better knowledge base. We know that sorafenib (Nexavar, Bayer/Onyx), which is currently approved for use in inoperable hepatocellular carcinoma, actually decreases levels of some anti-apoptotic proteins that cancer cells manufacture. Future therapy may allow us to administer a second medication that triggers the apoptotic process and stimulates the cell death of the cancer. The most promising approach is to administer TRAIL in conjunction with sorafenib. There is an ongoing phase I clinical trial in liver cell cancer patients, combining TRAIL agonists with sorafenib.

G&H Are there any other ways that knowledge of apoptosis can be applied in liver disease?

GG Another potential therapeutic pathway involves the promotion of apoptosis in the stellate cells in order to curb production of collagen and provide therapeutic treatment for fibrosis. This concept has not been as aggressively pursued as the others mentioned above, but I think it is important. It could potentially provide a method to halt fibrosis without damaging the overall function of the liver.

Suggested Reading

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